REMARKS

Claim amendments

Claims 79-101 have been canceled.

Claims 1, 17, 28, 33, 43, 51, 56, 66 and 74 have been amended to replace the phrase "other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based " with the phrase "a heterologous promoter which is not related to the promoter from the retrovirus upon which the retroviral vector is based". Support for the amendment can be found, for example, on page 10, lines 4-16 and Examples 1-3.

Claims 1, 17, 28, 56, 66 and 74 have been amended to delete the phrase "reduced chance of recombination".

Claims 5, 11, 12, 15, 38, 39, 61 and 62 have been amended to provide proper antecedent basis.

No new matter has been added.

5. Rejection of Claims 1, 5, 7, 9-26, 28, 29, 31, 32 and 56-78 under 35 U.S.C. §112, first paragraph

Claims 1, 5, 7, 9-26, 28, 29, 31, 32 and 56-78 are rejected under 35 U.S.C. §112, first paragraph as containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" (Office Action, page 3). The Examiner states that Applicants "have failed to note support" for the following added claim language: a heterologous promoter other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based (Office Action, page 3). The Examiner states that "[w]hile the specification provides an example of insertion of promoters from a cellular gene, it does not provide support for the claimed genus of retroviral promoters" (Office Action, page 3).

Applicants respectfully disagree. Nevertheless, in order to more clearly define the invention, Claims 1 and 56 have been amended to replace the phrase "other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the

retrovirus upon which the retroviral vector is based " with the phrase "a heterologous promoter which is not related to the promoter from a retrovirus upon which the retroviral vector is based". Support for the amendment can be found, for example, on page 10, lines 4-16 and Examples 1-3). In Examples 1-3 the promoter of the BAG vector, a murine leukemia virus vector (MoMLV), was replaced with two different heterologous promoters which are not related to the promoter from the retrovirus upon which the retroviral vector is based, *i.e.*, the MMTV promoter and the WAP promoter, are promoters that are not related to the promoter of the MoMLV vector.

At the time the application was filed, Applicants clearly had possession of the claimed invention, particularly as amended.

7. Rejection of Claims 1, 5, 7, 9-26, 28, 29, 31, 32 and 56-78 under 35 U.S.C. §112, second paragraph

Claims 1, 5, 7, 9-26, 28, 29, 31, 32 and 56-78 are rejected under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 4).

The Examiner states that Claims 1, 5, 7, 9-26, 28, 29, 31, 32 and 56-78 are indefinite for recitation of a heterologous promoter other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based (Office Action, page 4).

Applicants respectfully disagree. Nevertheless, in order to more clearly define the invention, Claims 1 and 56 have been amended to replace the phrase "other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based " with the phrase "a heterologous promoter which is not related to the promoter from a retrovirus upon which the retroviral vector is based". Support for the amendment can be found, for example, on page 10, lines 4-16 and Examples 1-3.

The Examiner states that there is insufficient basis in Claims 1, 5, 7, 9-26, 28, 29 and 31-101 for recitation of "said one or more sequences selected from coding sequences". The Examiner further states that the claims are indefinite because they read on vectors that comprise only non-coding sequences that further comprise promoters that regulate only coding sequences. The Examiner suggests amending the independent claims to recite only coding sequences.

The claims have been amended in accordance with the Examiner's suggestion.

The Examiner states that Claims 1, 5, 7, 9-26, 28, 29, 31, 32 and 56-78 are indefinite for recitation of "reduced chance of recombination".

The claims have been amended to delete this phrase.

The claims, particularly as amended, particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

9. Rejection of Claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72 and 74-78 under 35 U.S.C. §103(a)

Claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72 and 74-78 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Couture et al. in view of Faustinella et al." (Office Action, page 5). It is the Examiner's opinion that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vectors of Couture et al. by adding the multiple cloning site of Faustinella et al. because Faustinella et al. shows that multiple cloning sites may be used to insert sequences of choice in a U3 region of a retroviral vector" (Office Action, page 6). In response to Applicants' arguments in the previously filed Amendment, the Examiner states that Couture *et al.* show that "a variety of ***heterologous promoters*** have activity in the exemplified vectors (tables 1-3)" (Office Action, page 11, emphasis added).

Applicants respectfully disagree. Couture *et al.* substitute the U3 region of MoMLV with the corresponding region from ***related murine retroviruses***. In contract Applicants claim substituting the U3 region of the MoMLV with the corresponding region from an ***unrelated retrovirus***. The art of record does not motivate a person of skill in the art to substitute the U3 region of MoMLV with the U3 region of an unrelated retrovirus. Applicants' claimed invention has been amended to more clearly recite a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order: a 5' long terminal repeat region of the structure U3-R-U5; one or more sequences coding sequences, said sequences being inserted into the body of the vector; and a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing an ***unrelated***, heterologous promoter (*e.g.*, an

unrelated, heterologous retroviral promoter) is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences coding sequences.

The court has clearly stated that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention (*W.L. Gore & Associates, Inc. v. Garlock, Inc.,* 220 U.S.P.Q. 303 (Fed. Cir. 1983)).

Couture *et al.* describe retroviral vectors "in which the U3 promoter/enhancer of Moloney murine leukemia (MoMLV) was replaced by the corresponding region from ***five related murine retroviruses*** (AKV, HaMSV, MPSV, SL3-3 and Xeno) (Couture *et al.*, abstract, emphasis added). HaMSV has 99% LTR sequence homology, MPSV has 98% LTR sequence homology, AKV has 76% LTR sequence homology, SL3-3 has 74% LTR sequence homology; and Xeno has 64% LTR sequence homology with MoMLV (Couture *et al.*, Figure 2). Couture *et al.* show that except for activity of the AKV and SL3-3 chimeric LTR in JURKAT cells, in general, the lower the degree of homology between a particular ***related LTR sequence*** and the MoMLV LTR sequence, the lower the activity of the chimeric LTR (chLTR) vector in the infected cell (Couture *et al.*, Table 3). Couture *et al.* teach that:

> investigators performing retroviral-mediated gene transfer ***may*** benefit from the following ***suggestions***. In liver cells . . . either MPSV- or MoMLV-based vectors should be considered. . . In lymphoid cells, our data ***suggest*** that the SL3-3 chLTR vectors (and to a lesser extent, HaMSVchLTR vectors) would ***likely*** be more active than MoMLV vectors. Therefore, gene therapy approaches directed toward lymphocytic cell types would ***potentially*** be facilitated by the use of chLTR retroviral vectors based on the U3 region from SL3-3 (Couture *et al.*, page 675, column 2, emphasis added).

Thus, based on their observations, Couture *et al.* at most invite one of skill in the art to experiment with substituting the U3 region of MoMLV with the corresponding region from ***related murine retroviruses***. However, Couture *et al.* do not provide the suggestion or the motivation to substitute the U3 region of MoMLV with the corresponding region from ***unrelated retroviruses***, which would likely have even lower homologies with the MoMLV LTR sequence than the homologies of the 5 related sequences described in the Couture *et al.* reference. When the Couture *et al.* reference is considered in its entirety, Couture *et al.* would lead one of skill in the art away from substituting the U3 region of MoMLV with the U3 region of an unrelated

retrovirus. Consequently, Couture *et al.* cannot provide a reasonable expectation of success in doing so.

In a previous Office Action, the Examiner states that "Faustinella et al. is ***only cited for*** its teaching of a polylinker in the U3 region as a convenient structure to insert a desired sequence by recombinant DNA techniques" (Paper No. 33; Office Action dated May 6, 2002, page 13, emphasis added).

Clearly, the motivation to substitute the U3 region of MoMLV with the U3 region of an unrelated retrovirus is not present in the art of record. At most, the combined teaching of Couture *et al.* with Faustinella *et al.* would direct one of skill in the art to substitute the U3 region of MoMLV with the corresponding region from ***related murine retroviruses*** using a polylinker.

To establish a *prima facie* case of obviousness the following three basic criteria must be met: 1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or to combine reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference must teach or suggest all the claim limitations (*In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)). The Examiner has not established a *prima facie* case of obviousness. Applicants maintain that prior art combination of record has been made with the advantage of impermissible hindsight, and thus, the rejection is legally improper.

The combined teachings of Couture *et al.* and Faustinella *et al.* do not render obvious Applicants' claimed invention.

10. Rejection of Claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72 and 74-78 under 35 U.S.C. §103(a)

Claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72 and 74-78 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Couture et al. in view of Faustinella et al. . . . and further in view of Mee et al." (Office Action, pages 6-7). The Examiner states that Couture *et al.* in view of Faustinella *et* al. do not show MMTV promoters or regulatory elements (Office Action, page 7). It is the Examiner's opinion that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the

vector of Couture et al. in view of Faustinella et al. as applied . . . . above by insertion of an MMTV promoter region in a deleted 3' U3 region of a retroviral vector because Mee et al. show that their LTR promoter may be used to manipulate gene expression in a variety of cell types" (Office Action, page 7).

Applicants respectfully disagree. As pointed out above, the combined teachings of Couture *et al.* and Faustinella *et al.* do not render obvious Applicants' claimed invention. Mee *et al.* do not provide the teaching lacking in the Couture *et al.* and Faustinella *et al.* references. As discussed in the previously filed amendments, Mee *et al.* disabled the 3' LTR of a retroviral vector and cloned the HRE inducible promoter of the MMTV and the *aph* gene directly between the LTRs of the provirus, *i.e.,* into the body of the vector, producing a *self-inactivating (SIN) retroviral vector* (Mee *et al.*, pages 289-290). In contrast, Applicants teach a *non-SIN retroviral vector*. Mee *et al.* do not teach insertion of a promoter which is not related to the promoter of the retrovirus upon which the retroviral vector is based, into a partially deleted U3 region of a retroviral vector.

Clearly, the combined teachings of Couture *et al.*, Faustinella *et al.* and Mee *et al.* do not render obvious Applicants' claimed invention.

11. Rejection of Claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-35, 38, 39, 42-49, 51-55, 79-82, 84, 85, 88-95 and 97-101 under 35 U.S.C. §103(a)

Claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-35, 38, 39, 42-49, 51-55, 79-82, 84, 85, 88-95 and 97-101 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Couture et al. in view of Faustinella et al. . . . and further in view of Mehigh et al." (Office Action, page 7). The Examiner states that Couture *et al.* in view of Faustinella *et al.* do not show "cellular promoters or regulatory elements" (Office Action, page 7). It is the Examiner's opinion that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. in view of Faustinella et al. as applied . . . . above by insertion of a WAP promoter region in a deleted 3' U3 region of a retroviral vector because Mehigh et al. shows that such vectors are inducibly expressed and may allow for increased milk production in cattle" (Office Action, page 8).

Applicants respectfully disagree. As pointed out above, the combined teachings of Couture *et al.* and Faustinella *et al.* do not render obvious Applicants' claimed invention. The results of Couture *et al.* do not motivate a person of skill in the art to insert into a partially deleted U3 region of a retroviral vector, a promoter which is not related to the promoter of the retrovirus upon which the retroviral vector is based (e.g., an unrelated retroviral promoter or ***a promoter from a cellular gene (Claim 33)***).

Mehigh *et al.* do not provide the teaching lacking in the Couture *et al.* and Faustinella *et al.* references. Mehigh *et al.* fused the Whey acidic protein promoter (WAP) or the mouse mammary tumor virus (MMTV) promoter to the gene encoding synthetic bovine growth hormone-releasing factor (bGRF). Mehigh *et al.* teach that the plasmids "were able to induce transcription of bGRF upon transfection into . . . bovine kidney cells and induction with a lactogenic hormonal milieu . . . or dexamethasone" (Mehigh *et al.*, abstract). Mehigh *et al.* further teach that when the "constructs were cloned into a BLV vector in place of its oncogenic region, and transfected into MDBK cells, bGRF was expressed" (Mehigh *et al.*, abstract). Mehigh *et al.* do not teach insertion of a promoter from a retrovirus which is not related to the retrovirus upon which the vector is based, into a partially deleted U3 region of the retroviral vector.

Clearly, the combined teachings of Couture *et al.*, Faustinella *et al.* and Mehigh *et al.* do not render obvious Applicants' claimed invention.

12. Rejection of Claims 1, 13, 14, 33, 40, 41, 56, 63, 64, 79, 86 and 87 under 35 U.S.C. §103(a)

Claims 1, 13, 14, 33, 40, 41, 56, 63, 64, 79, 86 and 87 are rejected under 35 U.S.C. §103(a) as being unpatentable over Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mee *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.*; and further as evidenced by Miller *et al.* and Panganiban *et al.* (Office Action, page 8). The Examiner concludes that "the vectors of claims 13 and 14 are taught by the above cited combinations of references as evidenced by Miller et al. and Panganiban et al." (Office Action, page 9).

Applicants respectfully disagree. As pointed out above, the combined teachings of Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further

in view of Mee *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.* do not render obvious Applicants' claimed invention. The results of Couture *et al.* do not motivate a person of skill in the art to insert into a partially deleted U3 region of a retroviral vector, a promoter which is not related to the promoter of the retrovirus upon which the retroviral vector is based (e.g., an unrelated retroviral promoter or ***a promoter from a cellular gene (Claim 33) or a non-retroviral promoter (Claim 79)***).

The teachings of Miller *et al.* and Panganiban *et al.* do not provide the teaching that is lacking. As discussed in the previously filed amendments, Miller *et al.* designed "a set of retroviral vectors which facilitate cDNA transfer and expression" (Miller *et al.*, page 986, column 3), one of which is the LXSN retroviral vector used by Couture *et al.* to generate their vectors. Panganiban *et al.* ('84) mutagenized cloned spleen necrosis virus and showed that the 3' end of the *pol* gene of the spleen necrosis virus encodes a polypeptide required for DNA integration through interaction with the *att* site. Neither Miller *et al.* nor Panganiban *et al.* teach or even suggest a retroviral vector wherein the U3 region comprises a promoter *which is not related to a retrovirus upon which the retroviral vector is based* and which regulates expression of a coding sequence inserted into the body of the vector after infection of the target cell.

Clearly, the combined teachings of Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mee *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.* and further as evidenced by Miller *et al.* and Panganiban *et al.* do not render obvious Applicants' claimed invention.

13. Rejection of Claims 1, 10, 33, 37, 56, 60, 79, 83, 89 and 96 under 35 U.S.C. §103(a)

Claims 1, 10, 33, 37, 56, 60, 79, 83, 89 and 96 are rejected under 35 U.S.C. §103(a) as being unpatentable over Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mee *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.*; and further in view of Price *et al.* (Office Action, pages 9-10). It is the Examiner's opinion that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of the above cited combinations of references by basing the construction on a BAG vector of Price et al. because Price et al shows

that a vector with a beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector" (Office Action, page 10).

Applicants respectfully disagree. As pointed out above, the combined teachings of Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mee *et al.*; and Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.* do not render obvious Applicants' claimed invention. The results of Couture *et al.* do not motivate a person of skill in the art to insert into a partially deleted U3 region of a retroviral vector a heterologous promoter (e.g., a retroviral promoter, ***a promoter from a cellular gene (Claim 33) or a non-retroviral promoter (Claim 79)***) from an unrelated murine retrovirus.

The teaching of Price *et al.* does not provide the teaching that is lacking. As discussed in the previously filed amendments, Price *et al.* inserted the β-gal gene, the SV40 early promoter and the Tn5 *neo* gene into the body of the pDOL vector, which is derived from the Moloney murine leukemia virus (Mo-MuLV), and used the vector as a cell-lineage marking system applicable to the vertebrate nervous system. There is clearly no discussion in the Price *et al.* reference regarding the manipulation of the U3 region of the pDOL vector for any purpose.

Clearly, the combined teachings of Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mee *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.* and further in view of Price *et al.* do not render obvious Applicants' claimed invention.

14. Rejection of Claims 17, 20, 21, 26, 28, 43, 50, 51, 52, 53, 66, 73, 74, 75, 76, 89, 96, 97, 98 and 99 under 35 U.S.C. §103(a)

Claims 17, 20, 21, 26, 28, 43, 50, 51, 52, 53, 66, 73, 74, 75, 76, 89, 96, 97, 98 and 99 are rejected under 35 U.S.C. §103(a) as being unpatentable over Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mee *et al.*; Couture et al. in view of Faustinella et al. and further in view of Mehigh *et al.*; and further in view of Longmore *et al.* and Kay *et al.* (Office Action, page 10). It is the Examiner's opinion that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the teachings of the combinations of references cited above to express a therapeutic protein because Kay et al. and Longmore et al. show that retroviral vectors may be

used to express therapeutically effective levels of a recombinant protein in an animal" (Office Action, page 11).

Applicants respectfully disagree. As pointed out above, the combined teachings of Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mee *et al.*; and Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.* do not render obvious Applicants' claimed invention.

The teachings of Longmore *et al.* and Kay *et al.* do not provide the teaching that is lacking. As discussed in the previously filed amendments, Longmore *et al.* infected mice with a recombinant spleen focus-forming retrovirus (SFFV) expressing an oncogenic erythropoietin (Epo) receptor (EpoR) and showed a relationship between erythropoiesis and thrombopoiesis at the level of the Epo-EpoR signalling pathway. In addition, Longmore *et al.* teach that the SFV-based vectors "may be excellent vehicles for the introduction of genes into multipotent, hematopoietic progenitors, in vitro" (Longmore *et al.*, abstract). Using an amphotropic retroviral vector that encoded the canine factor IX complementary DNA, Kay *et al.* determined that a method for hepatic gene transfer *in vivo* by the direct infusion of recombinant retroviral vectors into the portal vasculature of a hemophilia B dog model, which results in the persistent expression of exogenous genes, may be feasible for the treatment of hemophilia B patients. There is no discussion in the Longmore *et al.* or Kay *et al.* references regarding the manipulation of the U3 region of their retroviral vectors for any purpose.

Clearly, the combined teachings of Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mee *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.* and further in view of Longmore *et al.* and Kay *et al.* do not render obvious Applicants' claimed invention.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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Dated: December 17, 2003